April 26, 2006

Mr. John Morris
American Chemistry Council
Aliphatic Esters Panel
1300 Wilson Boulevard
Arlington, VA 22209

Dear Mr. Morris:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Diesters Category posted on the ChemRTK HPV Challenge Program Web site on January 6, 2004. I commend the Aliphatic Esters Panel for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Panel advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission. Please send any electronic revisions or comments to the following e-mail addresses: oppt.ncic@epa.gov and chem.rtk@epa.gov.

If you have any questions about this response, please contact Mark Townsend, Chief of the HPV Chemicals Branch, at 202-564-8617. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

/s/

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: W. Penberthy
J. Willis

EPA Comments on Chemical RTK HPV Challenge Submission:
Diesters Category

Summary of EPA Comments

The sponsor, the American Chemistry Council's Aliphatic Esters Panel, submitted a test plan and robust summaries for the revised Diesters Category, dated November 14, 2003. EPA posted the submission on the ChemRTK HPV Challenge Web site on January 6, 2004. The category consists of 13 substances. Four other substances were submitted as analogs for the category members.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Definition. The category definition is adequate.

2. Category Justification. The submitter's category rationale is generally reasonable. The inclusion of the bis[2-(2-butoxyethoxy)ethyl] ester of adipic acid in the category is inadequately supported. This compound is significantly different from the other C22 aliphatic diesters in the category, and no confirmatory data were provided for the health or ecotoxicity endpoints.

3. Analog Justification. Similarities among category members and analogs generally support the use of the analogs.

4. Physicochemical Properties. The submitter needs to provide measured melting point, vapor pressure, and water solubility data for several of the chemicals in this category.

5. Environmental Fate. The submitter needs to provide measured ready biodegradation data for adipic acid, bis[2-(2-butoxyethoxy)ethyl] ester.

6. Health Effects. Adequate data were not submitted for the full carbon number range of the category. However, the submitted data suggest that the trend indicating increasing toxicity with decreasing carbon number would extend to the lowest carbon-content category member. Therefore, adequate data were submitted to address all appropriate SIDS-level endpoints for the purposes of the HPV Challenge Program, except for the bis[2-(2-butoxyethoxy)-ethyl] ester of adipic acid (see Category Justification). The submitter needs to address deficiencies in the robust summaries.

7. Ecological Effects. The submitted data are not adequate for acute/chronic toxicity to fish, invertebrates or algae for the purposes of the HPV Challenge Program. Measured data need to be provided on a representative category member for all ecological endpoints in the lower molecular weight range (C12) and in the mid-molecular weight range (C14-16). Further testing is not needed for the high molecular weight range (C22-32). Data for the bis[2-(2-butoxyethoxy)ethyl] ester of adipic acid, and support for its inclusion in the category, are inadequate. The submitter needs to address deficiencies in the robust summaries.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA Comments on the Diesters Category Challenge Submission

Category Definition

This submission covers 13 aliphatic diesters of maleic (C4), adipic (C6), azelaic (C9), and sebacic (C10) acids. The esters range in total carbon number from C12 to C32. The sponsored diesters are: bis(1,3-dimethylbutyl) maleate (CAS No. 105-52-2), bis(2-ethylhexyl) maleate (CAS No. 142-16-5), diisopropyl adipate (CAS No. 6938-94-9), diisooctyl apidate (CAS No. 1330-86-5), bis(1-methylheptyl) apidate (CAS No. 108-63-4), diisononyl adipate (CAS No. 33703-08-1), diisodecyl adipate (CAS No. 27178-16-1), bis[2-(2-butoxyethoxy)ether] ester of adipic acid (CAS No. 141-17-3), ditridecyl adipate (CAS No. 16958-92-2), bis(2-ethylhexyl) azelate (CAS No. 103-24-2), diisodecyl azelate (CAS No. 28472-97-1), dimethyl sebacate (CAS No. 106-79-6), and bis(2-ethylhexyl) sebacate (CAS No. 122-62-3).

Category Justification

The submitter's rationale for grouping the sponsored compounds as a category is generally reasonable. However, there are significant differences between the structure and the estimated physicochemical values provided by the submitter for the bis[2-(2-butoxyethoxy)ethyl] ester of adipic acid (the only polyether in the category) and those of other category members; and because no data were provided for the health effects or ecotoxicity endpoints of this substance, its toxicity in relation to the other category members is unknown. Therefore, no basis for its inclusion in the category is evident. The submitter needs to better justify its inclusion in the category or submit it as a separate chemical.

Analog Justification

The four supporting substances are aliphatic diesters ranging in carbon number from C12 to C22: dibutyl maleate (CAS No. 105-76-0), dibutyl adipate (CAS No. 105-99-7), di-C7-9 branched and linear alkyl esters of adipic acid (CAS No. 68515-75-3), and bis(2-ethylhexyl) adipate (CAS No. 103-23-1). From the structural similarities and the pattern of measured physicochemical properties, EPA agrees that the submitted analog data can be used to evaluate corresponding category members.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility)

The data provided by the submitter for boiling point and partition coefficient are adequate for the purposes of the HPV Challenge Program.

Melting Point. The estimated data provided by the submitter for adipic acid, bis(1-methylheptyl) ester; adipic acid, bis[2-(2-butoxyethoxy) ethyl] ester; adipic acid ditridecyl ester, and azelaic acid, diisodecyl ester are not adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured data for melting point values above 0 °C.

Vapor Pressure. The estimated data provided by the submitter for maleic acid, bis(1,3-dimethylbutyl) ester; maleic acid, bis (2-ethylhexyl) ester; adipic acid, diisopropyl ester; adipic acid, bis (1-methylheptyl) ester; adipic acid, bis [2-(2-butoxyethoxy) ethyl] ester; adipic acid, ditridecyl ester; azelaic acid, bis (2-ethylhexyl) ester; azelaic, diisodecyl ester; sebacic acid, dimethyl ester; and sebacic acid, bis (2-ethylhexyl) ester are not adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured data for vapor pressure values above 7.5×10^{-8} mm Hg.

Water Solubility. The estimated data provided by the submitter for maleic acid, bis(1,3-dimethylbutyl) ester; adipic acid, diisopropyl ester; and adipic acid, bis[2-(2-butoxyethoxy)ethyl] ester are not adequate for the purposes of the HPV Challenge Program. The submitter needs to provide measured data for water solubility values above 1µg/L (1ppb).

Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)

The data provided by the submitter for photodegradation, stability in water, and fugacity are adequate for the purposes of the HPV Challenge Program.

Biodegradation. The data provided by the submitter are adequate for the purposes of the HPV Challenge Program, except for adipic acid, bis[2-(2-butoxyethoxy)ethyl] ester. The submitter did not provide data for this chemical. Because this chemical is structurally different from the other category members, the submitter needs to provide measured ready biodegradation data following OECD TG 301.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)

General. As discussed above in the Category Justification section, the inclusion in the category of the bis[2-(2-butoxyethoxy)ethyl] ester of adipic acid is not supported for the health effects endpoints.

Adequate data were submitted for all appropriate SIDS-level endpoints, for the mid to high carbon number range of the category, for the purposes of the HPV Challenge Program. Because no data were provided for dimethyl sebacate, data are not available for the low carbon number range, and therefore across the full carbon number range of the category (dibutyl maleate is not an adequate analog for the sebacate because of the differences in structure). However, data for category members and analogs show consistently low acute toxicity and negative mutagenicity but positive reproductive/developmental toxicity, suggesting that the trend indicating increasing toxicity with decreasing carbon number would extend to the lowest carbon-content category member. Therefore, no further testing is needed for the purposes of the HPV Challenge Program.

Repeated-Dose Toxicity. There are discrepancies between the data provided in the test plan and in the robust summaries for bis(2-ethylhexyl) sebacate. Robust summaries need to be provided for a 19-month oral diet study and for a 20-day reproductive/developmental toxicity screen of ditridecyl adipate in rats, both listed in Table 3 of the test plan. Further, it would be helpful to include any available data on the dermal absorption of the substance in these robust summaries, to validate the data submitted for the reproductive toxicity endpoint.

Ecological Effects (fish, invertebrates, and algae)

All the submitted data on sponsored chemicals are inadequate because the reported toxicities are all above the water solubility limits of the tested chemicals.

No measured data were provided for acute toxicity to fish, invertebrates and algae for the lower molecular weight diesters (e.g., C12). In the absence of adequate analog data (see below) the submitter needs to provide measured acute toxicity data for fish, invertebrates, and algal endpoints on diisopropyl adipate to establish the lower acute toxicity boundaries for these endpoints. The submitter also needs to test for acute and chronic toxicity on bis(1,3-dimethylbutyl) maleate to clarify the trend from acute to chronic toxicities. Although the submitted data are inadequate for the higher molecular weight range (C20-32), EPA recommends no testing because of the high log Kow and low water solubility of these chemicals.

As discussed above in the Category Justification section, the inclusion in the category of the bis[2-(2-butoxyethoxy)ethyl] ester of adipic acid is not supported. As presented, only measured data will suffice for this ester.

For all analogs, only the toxicity values were provided, with no robust summaries. For the analog data to be considered, the submitter needs to provide robust summaries for these studies, especially for dibutyl maleate, the only analog supporting the lower molecular weight diesters (C12).

Specific Comments on the Robust Summaries

General

The following comments apply to all the robust summaries provided by the submitter. In general, the robust summaries do not provide sufficient detail. The submitter should consult EPA guidance documents for the preparation of robust summaries (http://www.epa.gov/opptintr/chemrtk/guidocs.htm).

Health Effects

Acute Toxicity. Study details missing include test substance purity and frequency of body weight determinations.

Repeated-Dose Toxicity. Study details missing include test substance purity and a full list of organs weighed and tissues examined microscopically.

Genetic toxicity (gene mutations). Study details missing include test substance purity, statistical methods used, if any, cytotoxic concentration (if observed), and mean number of revertants per concentration.

Genetic toxicity (chromosomal aberrations). Study details missing include the interval between last dosing time and collection of blood and bone marrow.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.